REMARKS

I. Status of the Claims

Claims 11, 17 and 20 are amended

Claims 10-12, 16, 17 and 20 are pending.

II. A *Prima Facie* Case of Obviousness is Not Established

Claims 10-12, 16, 17 and 20 were rejected under 35 U.S.C. §103(a) over Mitsuhashi, Ash et al. (1991 and 1992), Chee et al. (1996) and Genbank Accession Nos. (GI Nos) 3929652, 8452887, 3929664, 3929662, 927390 and 1149455.

A *prima facie* case of obviousness is not established.

The examiner admits the deficiencies in each of the cited publications:

> Mitsuhashi does not teach probes corresponding to the specific oligonucleotide probes of claim 10.

Office Action, page 4:

Misuhashi relates to fungi, not bacteria, and teaches use of a single polynucleotide probe, optionally on a solid support, wherein the probe is "complementary to a sequence of ribosomal RNA (rRNA) specific to the particular species of fungus." (Abstract) The rRNA in the sample "only hybridizes with a sequence contained in the ribosomal RNA of the particular species of fungus." The patent also relates a "second, labeled probe" which "can be used." (Field of Invention)

Claim 10 relates a microarray with probes from *Bacillus*, and claim 20 relates a kit having the probes. The examiner admits Mitsuhasi does not teach any of these probes. The examiner cites Mitsuhashi for a **method**, but neither claim 10 nor 20 relates a method, so the Mitsuhashi publication as the examiner uses it - is not relevant to claims 10 and 20.

Ash only related some difference among *Bacillus* sequences, and did not teach distinguishing *Anthracis*. As the examiner admits:

> Ash does not teach the specific obligonucleotide probes of clam 10 or the use of a microchip, hybridization, or analysis of hybridization signals for distinguishing among the members of the *B cereus* group.

Office Action, page 4:

The examiner cites to Ash as teaching "a method of discrimination" among *Bacillus* "based on 16s RNA sequencing." Claim 10 is compositions, not methods.

Chee is also cited for a "method" not the claimed composition. Chee relates analysis of human mitochondrial DNA, not *Bacillus* and not rRNA. Also, the cite on page 5 of the Office Action is so indefinite on its face as to be useless to those of skill in the act and enables nothing. The examiner admits:

> Chee does not teach the use of such an array for the discrimination among members of the *B. cereus* group, but does teach that '[t]he methods described are generic and can be used to address a variety of questions in molecular genetics including gene expression,' genetic linkage and genetic variability" (see Abstract).
>
> Chee does not teach the use of the specific obligonucleotide probes of claim 10.

Office Action, pages 4 and 5:

The examiner sloughs off probe design as justification for those claimed as obvious because of Ash giving an opinion that "small subunits in RNA" are useful, and because full sequences of *Bacillus* are known. Ash's finding of 99-100% similarity in 16S rRNA suggested rRNA sequences might not be useful for discrimination of the *B. cereus* group. Inconsistencies were found between Ash's sequences and those that formed the basis of the present probes. The gene bank accession numbers relate large sequences - there is no guidance cited by the examiner that would lead to the claimed probes. The design and composition of the claimed probes is not obvious, nor has the examiner even attempted to show they are.

The present invention is different from the combination of the cited publications because the inventor presents a novel hierarchy of probes that distinguish *B. anthracis* (see FIGs. 1-3 for taxonomic relations, FIG. 4, 8, for examples of design.) Strain and subgroup specific signature profiles of 16S and 23S rRNA were developed. The claimed microarrays are based on those profiles. The U.S. Patent Office has forced applicant to reduce the number of 16S and 23S RNA

probes claimed that optimize the invention, to 10. This artificial selection does not give full scope to the invention. Instead of a full array on a microchip as shown in the Summary, claims had to be amended to only show the five pairs of probes. However, the probes were developed due to the analysis of signature profiles and will still discriminate. However, that set of 10 is, by the examiner's admission, still not contained in the compilation of publications and nucleotide sequences cited. Therefore, even were the publications and sequences properly combined, the combination does not yield the claimed invention.

16S and 23S rRNA targeted oligonucleotide probes were designed to discriminate among the seven subgroups within *B. cereus*, in particular to discriminate *B., anthracis* from other subgroups.

The hierarchy of probes used to differentiate among *Bacillus* subgroups is shown in FIG. 1 (16S rRNA) and FIG. 2 (23S rRNA). This is the first systematic analysis of the *B., cereus* group. Phylogenetic trees that are the basis of discriminatory probe selection are shown in FIG. 3. Probes are in Table 5.

FIG. 4 (16S rRNA) and FIG. 5 (23S rRNA) show microchip identification of *Bacillus* species.

FIG. 6-8 illustrate use of the invention. In FIG. 4 ps/ps2, ps3/ps4, ps5/ps6, ps7/ps8 distinguish Thurenegensis A from B.

An embodiment of a microchip is given on pages 10-11 - "10 pairs of oligonucleotide probes that target 16S rRNA sequences and two pairs of oligonucleotide probes targeting 23S rRNA sequences wherein the oligonucleotide are selected from Table 5. An example of a microchip design is in FIG. 8.

Microchips shown in FIG. 4 and FIG. 8 are capable of discriminating all seven subgroups of the *B. cereus* group.

Only 2 of the 22 16S rRNA and 23S rRNA gene sequences were published previously. Discrepancies with these sequences are discussed on page 15 of the application and were likely due to errors in the art.

The 10 probes in pending claims are not randomly selected. (All are in Table 5.)

FIG. 4 illustrates what ps5/ps6, ps17/ps18, and ps19/ps20 are used to identify when on a

16S rRNA microchip;

FIG. 5A, B, illustrate what ps21/ps22 are used for on a 23S rRNA microchip (differentiating members of the Cereus A subgroups from the Anthracis subgroup);

FIG. 6 illustrates what ps17/ps18 can identify in a 16S rRNA subgroup mixture;

FIG. 8 illustrates 23FI (not MYC A, B) and 23F2 (MYC A, B) used in a microchip map.

With regard to claims 11 and 12 - **of course**, it is a matter of design - the design is part of the novelty of the present invention.

Incredibly, the examiner applies his own reasoning, based on hindsight, to construct a story that the claimed probes would have been designed by those of skill in the act by putting "variant nucleotides identified by Ash" in the middle of probes, because of the teachings of Chee. Chee relates polymorphism as evidence of genetic variation within species. The probes of the present invention detect variations **among** species. The examiner admits some problems with his logic, citing *In re Deuel*. His reliance is misplaced because no probes with the "structural similarity" required by *In re Deuel* are cited by the examiner, no "functional homologs" are cited.

Obviousness requires a suggestion of all limitations in a claim. *CFMT, Inc. v. YieldupInt'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003) To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.* 776 F. 2d 281 (Fed. Cir. 1985); Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicants disclosure. *In re Vaeck* 947 F. 2d 488 (Fed. Cir. 1991). The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* 229 F. 2d 476 (CCPA 1956); *In re Skoll* 523 F. 2d 1392 (CCPA 1975); in *In re Rouffet* the court held: To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the

inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

One cannot simply backtrack from the invention to find a connection to the prior art. Hindsight must be avoided. See *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Rather, one must start with the prior art and find some suggestion or motivation either in a single reference to modify it to produce the claimed invention, or some suggestion or motivation in a group of references to combine them to produce the claimed invention. *Nursery Supplies v. Lerio Corp.*, 45 U.S.P.Q.2d (BNA) 1332 (M.D. Pa. Sept. 19, 1997)

IV. Other Issue

A terminal disclaimer will be filed after claims are allowed.

Claims are amended to correct format as suggested.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21416-94731).

Respectfully submitted,

BARNES & THORNBURG

Alice O. Martin
Attorney Registration No. 35,601

BARNES & THORNBURG LLP
P.O. Box 2786
Chicago, Illinois 60690-2786

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